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Diffusion-Weighted Magnetic Resonance Imaging for Diagnosis of Liver Fibrosis and Inflammation in Chronic Viral Hepatitis: The Performance of Low or High b Values and Small or Large Regions of Interest

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Abstract

Objective: To investigate the performance of different b values and regions of interest (ROI) for diagnosing liver fibrosis in patients with chronic viral hepatitis by using diffusion-weighted (DW) magnetic resonance imaging (MRI).

Methods: Eleven healthy participants and 33 patients with viral hepatitis B or C were enrolled. The stage of liver fibrosis and the grade of necroinflammation were determined by using a histologic activity index. Single-shot spin-echo echo-planar DW-MRI was performed in all participants at b values of 0-500, 0-700, and 0-1000 s/mm^2 by using 2 circular small and large ROIs of 100 and 200 mm^2. To evaluate the performance of different b values for determining cirrhosis, the receiver-operating characteristic curves were depicted, and the areas under the curves were compared.

Results: The average values of apparent diffusion coefficients significantly decreased with increasing stage or grade categories at all the 3 b values and for both small and large ROIs. The performance at b = 500 s/mm^2 was significantly better than b = 1000 s/mm^2 for determining cirrhosis or bridging fibrosis. The cut point of 153.4 for apparent diffusion coefficient ($\times 10^{-5}$ mm^2/s) at b = 500 s/mm^2 could determine cirrhosis or bridging fibrosis with a sensitivity of 96% and specificity of 82%. No difference was found between the average apparent diffusion coefficient values of large or small ROIs. Also, there was no difference in performance of large or small ROIs in the diagnosis of liver fibrosis.

Conclusions: This study provided beneficial data for clinical utilisation of DW-MRI in diagnosing liver fibrosis: b = 500 s/mm^2 is better in performance than b = 1000 s/mm^2, and a small ROI of 100 mm^2 is sufficient for determining cirrhosis or bridging fibrosis.

Résumé

Objectif : Étudier le rendement de différentes valeurs b et régions d'intérêt (ROI) pour diagnostiquer la fibrose du foie chez des patients atteints de l'hépatite virale chronique au moyen d'imagerie de diffusion par résonance magnétique (IRM).

Méthodes : L'étude portait sur 11 participants en santé et 33 patients atteints de l'hépatite virale B ou C. Le stage de la fibrose du foie et le degré d'inflammation hépatique ont été déterminés au moyen d'un indice d'activité histologique. Des clichés pondérés d'IRM de diffusion ont été effectués par séquence d'écho de spin d'imagerie échoplanaire chez tous les participants ayant des valeurs b de 0 à 500, de 0 à 700 et de 0 à 1 000 s/mm2 sur deux régions d'intérêt circulaires, soit une petite et une grande, respectivement de 100 et de 200 mm2. Pour évaluer le rendement de différentes valeurs b afin de déterminer la cirrhose, les fonctions d'efficacité du récepteur ont été illustrées et les régions sous les courbes ont été comparées.

Résultats : Les valeurs moyennes des coefficients de diffusion apparents affichaient une baisse importante lorsque les catégories de stade ou de degré des trois valeurs b augmentaient, et ce, tant pour les petites et que les grandes régions d'intérêt. Afin de déterminer la cirrhose ou la

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fibrose en pont, le rendement où b = 500 s/mm2 était de loin supérieur à celui où b = 1 000 s/mm2. Le point de coupure de 153,4 pour le coefficient de diffusion apparent (×10−5 mm2/s) où b = 500 s/mm2 peut déterminer la cirrhose ou la fibrose en pont avec une sensibilité de 96 % et une spécificité de 82 %. Aucune différence n'a été relevée entre les valeurs moyennes du coefficient de diffusion apparent des petites et des grandes régions d'intérêt. En outre, les deux types de régions d'intérêt n'affichaient pas de différence de rendement quant au diagnostic de la fibrose hépatique.

Conclusions : Cette étude a produit des données très utiles pour l'utilisation clinique l'IRM de diffusion en vue de diagnostiquer la fibrose du foie : b = 500 s/mm2 produit un meilleur rendement que b = 1 000 s/mm2, et une petite région d'intérêt de 100 mm2 suffit pour déterminer la cirrhose ou la fibrose en pont.

Key Words: Diffusion weighted; Magnetic resonance imaging; Cirrhosis; Viral hepatitis; Liver fibrosis; Histologic activity index

Liver fibrosis is a histologic feature that can finally lead to liver cirrhosis in patients with chronic viral hepatitis [1]. Because the severity of fibrosis affects the patient's management, outcome, and the need to antiviral treatment, the exact identification of the stage of liver fibrosis is of utmost importance [2]. Percutaneous liver biopsy has traditionally been used as the criterion standard method for evaluating the severity of fibrosis in patients with chronic liver disease [3]. However, it is an invasive procedure with poor patient acceptance, a rate of 0.3% for major complications, and the possibility of sampling errors [4,5]. Therefore, numerous efforts have been made to use noninvasive methods in quantification of liver fibrosis [6]. Transient elastography or biochemical scores, including aspartate aminotransferase to platelet ratio index or a FibroTest, have all been proposed for this goal, but their role in clinical practice is currently being investigated [7,8].

Diffusion-weighted (DW) magnetic resonance imaging (MRI) is an emerging tool in evaluating the stage of fibrosis [9−11]. This technique quantifies the combined effects of microcirculation of blood (perfusion) and molecular Brownian motion of water (diffusion) in liver parenchyma by means of apparent diffusion coefficients (ADC) [12]. Several researchers have mentioned that ADC values are significantly lower in patients with cirrhosis, with this reasonable explanation that fibrotic changes in liver parenchyma would restrict the motion of water molecules [13,14]. Nonetheless, disparities in the technical settings, the amount of b values (the combination effect of strength and duration of the gradients taken into account throughout the spin-echo evolution intervals) and the patient populations have led to inconsistent findings. Previous studies have used various ranges of b values for studying liver fibrosis [13−15]. Despite this, less evidence is available about the comparative performance of these b values in determining liver fibrosis. Also, previous studies have investigated liver fibrosis in different regions of interest (ROI), ranging from 50-173 mm^2 [11,16,17]. However, the influence of choosing small or large ROIs on determining liver fibrosis has not been addressed before. The aim of the present study was to investigate the performance of 3 different b values (0-500, 0-700, and 0-1000 s/mm^2) and 2 different ROIs (100 and 200 mm^2) for a diagnosis of liver fibrosis in patients with chronic viral hepatitis by using DW-MRI.

Methods

Participants

A total of 11 healthy subjects and 33 patients with viral hepatitis B (n = 17) or C (n = 16) were enrolled in this study. The patients were consecutively and prospectively enrolled from those who were admitted to the gastroenterology ward of a large university general hospital. Healthy volunteers were recruited from the healthy participants who regularly visited at general clinic of the same hospital. The mean age (± standard error of the mean [SEM]) of healthy controls (2 women [18%]) and of patients (4 women [12%]) was 38.87 ± 3.84 and 37.93 ± 2.29 years, respectively. The research was carried out according to the principles of the Declaration of Helsinki. The local ethics review committee of our university approved the study protocol. All the participants gave written informed consent before sampling.

To minimize the probable effect of steatosis [18], liver ultrasonography (Sonoline Antares; Siemens, Erlangen, Germany) was performed by a single experienced radiologist, and the participants with evidence of fatty liver [19] were excluded. None of the participants were alcohol users, and none of them had a history or clinical evidence of liver diseases other than chronic viral hepatitis. The diagnosis of hepatitis B and C infection was based on consistent clinical findings, serologic markers, hepatitis B virus DNA, and hepatitis C virus RNA measurements by the polymerase chain reaction method and histologic examinations (liver biopsy). None of the patients were under treatment for hepatitis B or C infection. Antibodies to hepatitis C virus, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis B e antigen, and hepatitis B e antibody were measured by using commercially available enzyme-linked immunosorbent assay kits (DRG Diagnostics GmbH, Marburg, Germany). All the healthy participants had normal liver transaminases and negative markers of hepatitis B and C infection. Liver biopsy was performed in the right liver lobe in all the patients (n = 33) as a part of their routine clinical care, and the samples were reported by one experienced pathologist. The stage of liver fibrosis (0-6, none; portal fibrosis, some; portal fibrosis, most; bridging fibrosis, few; bridging fibrosis, many; incomplete cirrhosis; and cirrhosis), and the grade of necroinflammatory activity (0-18) was determined by

using the histologic activity index (HAI) [20]. In this index, the grade of necroinflammatory activity is determined based on the degree of periportal necrosis, including piecemeal necrosis and/or bridging necrosis, the degree of bridging necrosis, the degree of hepatocyte degeneration and focal necrosis within the lobule, and the degree of portal inflammation. The patients, who were consecutively referred from the gastroenterology ward, were enrolled in 1 of the 3 categories of liver fibrosis (portal fibrosis, stage 1 or 2; bridging fibrosis, stage 3 or 4; and cirrhosis, stage 5 or 6), based on the predetermined sample size (n = 11 in each category).

Diffusion-Weighted Imaging

MRI measurements were performed on a GE Signa 1.5 T (GE Medical Systems, Milwaukee, WI). DW-MRI data were acquired before biopsy (4-14 days; in 4 of the patients) or at least 1 month after biopsy (30-60 days; in 29 of the patients) to avoid the potential effect of the procedure on the images. By performing a routine respiratory-gated axial fast spin-echo T2-weighted sequence of whole liver in all the participants, we excluded patients with any focal liver lesions (n = 2) before the DW imaging (DWI). A body coil was used for all experiments, with participants in the supine position. Six slices in the middle portion of the liver (with a localizer in the coronal plane for slice placement) were obtained (with 6-mm thickness and spacing of 2 mm). The participants were asked to hold their breath during each DW-MRI acquisition, which was less than 20 seconds (the acquisition time was between 16 and 17 seconds). Also a technician was monitoring the respiratory movements of the patients during image acquisitions by looking at the monitor for respiratory wave pattern changes; in case of any accidental or unintentional breathing during examination, a repeated examination was requested. Three breath-hold acquisitions were performed in the same liver locations at b values of 0-500, 0-700, and 0-1000 s/mm^2, with tridirectional diffusion gradients. Acquisition parameters of DW-MRI were the following: single-shot spin-echo echo-planar DW-MRI, repetition time = 1000, echo time = minimum, matrix size = 128 × 128, field of view = 40, number of excitation = 4, band widths = 62 kHz. Analysis of DW-MRI data were performed with the GE FUNCTOOL software (GE Medical Systems) to obtain ADC maps at each b value (500, 700, and 1000 s/mm^2). We selected the best 3 slices in the right lobe of the liver, far from the diaphragm, vessels, and ducts, mainly at segments 5 and 6. Two experienced observers placed ROIs in the most appropriate locations; far from the diaphragm, vessels, and ducts, in each selected slice. Two different sizes of circular ROIs (small, 100 mm^2; and large, 200 mm^2) were applied in each slice. For either large or small ROIs, the average of the 3 mean ADC numbers of the 3 selected slices was considered as the ADC value of participant. The axial echo-planar diffusion-weighted images of a liver at b values 500 and 1000 s/mm^2 are demonstrated in Figure 1. Although the quality of the images somewhat decreases with an increase in b value, the ADC map is more homogeneous and easier to use on higher b-value images.

Statistical Analysis

Statistical analysis was performed by SPSS software (version 18.0; SPSS Inc, Chicago, IL). The required sample size to detect a significant association at $\alpha = .05$ and with a power of 80% was estimated to be 11 in each 2 neighbouring groups of HAI of liver fibrosis (portal fibrosis, stage 1 or 2; bridging fibrosis, stage 3 or 4; and cirrhosis, stage 5 or 6). Continuous variables are expressed as mean ± SEM. The value of ADC was compared among different stage or grade groups by using analysis of variance and the post hoc Tukey test. The method of general linear modelling was used to compare the adjusted values of ADC among different grade or stage categories. The level of association between the grade or stage and other variables was measured by using Spearman rank order correlation coefficients. To compare the performance of different b values for determining patients with cirrhosis, the receiver-operating characteristic (ROC) curves were depicted and the area under the curves (AUC) were compared by using STATA software (version 9.0; StataCorp, College Station, TX). The shortest distance value from the point (0,1) ($[1 - \text{sensitivity}]^2 + [1 - \text{specificity}]^2$) on the ROC curve [21] was determined as the optimal cut point of ADC for determining cirrhosis or bridging fibrosis in different b values. $P < .05$ was considered statistically significant.

Results

No difference was found in age and sex ratio between healthy controls and patients (mean [± SEM] age, 38.87 ± 3.84 years vs 37.93 ± 2.29 years; and women/men, 2/9 vs 4/29, respectively) and among different stages of liver fibrosis. The mean (SEM) of stage of liver fibrosis and grade of necroinflammation in the patients group were 3.45 ± 0.34 and 8.75 ± 0.58, respectively.

The ADC Values in Different Stages and Grade Categories by Using Different b Values and ROIs

The mean value of ADC ($\times 10^{-5}$ mm^2/s) in different stage and grade categories according to different b values (s/mm^2) are presented in Table 1. No significant difference was found in the average ADC values of participants between the large and small ROIs at all 3 b values. The average ADC values significantly decreased from the control group to the patients with higher grades or stages of cirrhosis in both large and small ROIs and in all the 3 different b values. When considering the data of different b values and different ROIs together, the percentage of reduction in the average ADC value (in comparison with the control group) was approximately 10% in patients with bridging fibrosis and approximately 15% in patients with cirrhosis. Although higher-grade categories were significantly associated with lower ADC values, this association completely disappeared after adjustment for the stage of fibrosis ($P > .05$) in all different b values and for both small and large ROIs. However, the association between stage categories and ADC values was independent

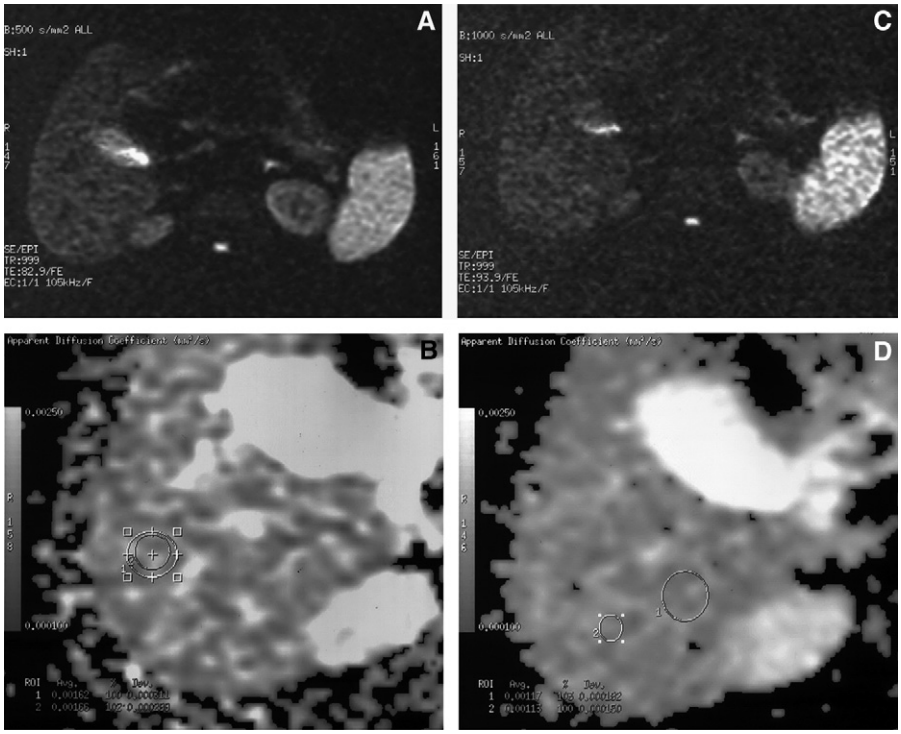

Figure 1. Axial echo-planar diffusion-weighted images (DWIs) of the liver at b values of 500 and 1000 s/mm^2, and their corresponding apparent diffusion coefficients (ADC) maps in a 53-year-old man with chronic hepatitis B (stage I on biopsy): (A) DWI at b = 500; (B) the corresponding ADC map (ACD value with small regions of interest [ROI], 1.66 mm^2/s; ACD value with large ROI, 1.62 mm^2/s); (C) DWI at b = 1000; and (D) the corresponding ADC map (ACD value with small ROI, 1.13 mm^2/s; ACD value with a large ROI, 1.17 mm^2/s).

of grade and remained significant after adjustment for grade of inflammation.

The Association Between ADC Values and Stage or Grade Scores

The grade and stage of fibrosis were significantly correlated ($r = 0.604$, $P < .001$). The association between the ADC values and the stage of fibrosis and grade of inflammation in patients are presented in Table 2. These associations were generally stronger in the lowest b value (500 s/mm^2). For example, no association was found between grade and ADC in the b value of 1000. The associations between stages of liver fibrosis and ADC values were independent of grade at different b values and ROIs; however, the associations between the grades and ADC values lost their significance after adjustment for stage of fibrosis.

Optimal Cut Points for Determining Cirrhosis and Bridging Fibrosis

ROC analysis showed that there was a significantly ($P < .05$) better performance for b = 500 in comparison with b = 1000 for determining stage ≥ 5 (cirrhosis: mean [± SEM] AUC, 0.86 ± 0.06 vs 0.72 ± 0.09, respectively) and stage ≥ 3 (cirrhosis or bridging fibrosis: mean [± SEM] AUC, 0.92 ± 0.041 vs 0.79 ± 0.07, respectively) by using small or large ROIs. No difference was found between the performances of large or small ROIs in the diagnosis of liver fibrosis at each of the 3 b values. Because there were almost similar results for small or large ROIs, we only presented our results for small ROIs (Figure 2). The optimal cut point of ADC values for determining stage ≥5 (cirrhosis) and stage ≥3 (cirrhosis or bridging fibrosis) in different b values, by using small ROIs, are presented in Table 3.

Discussion

Histopathologic feature is an important factor to assess the patient's prognosis and the need for antiviral therapy in chronic viral hepatitis [22]. Percutaneous liver biopsy is the criterion standard method to evaluate the stage of fibrosis and grade of necroinflammatory changes in these patients [23]. Nonetheless, liver biopsy is not free of risk and is associated with the need for hospitalization and patient discomfort [4]. Conventional MRI did not show satisfactory results in the evaluation of disease activity in chronic hepatitis [24]. Numerous efforts have been made to describe magnetic resonance (MR) diagnostic criteria to quantify the liver pathologic changes [25]. For example, the caudate-to-right lobe ratio of more than 0.90, measured on gadolinium-enhanced images, showed sensitivity and specificity of 71.7% and 77.4%, respectively, in diagnosing patients with cirrhosis [25]. Another example is MR elastography, which is a new technique for staging of liver fibrosis [26]. It is reported that MR elastography is superior to biochemical testing with aspartate aminotransferases−to−platelet ratio index [27]. In a study by Huwart et al [27], it was shown that

Table 1
The average value of apparent diffusion coefficients (ADC) ($\times 10^{-5}$ mm^2/s) in different stages and grade categories according to different b values and small or large regions of interest

	Mean (± SEM) b value (s/mm^2)[a,b,c]					
	500		700		1000	
	Small	Large	Small	Large	Small	Large
Stage categories						
Control (n = 11)	168.2 ± 3.3	166.6 ± 3.5	141.9 ± 1.6	140.5 ± 1.8	113.7 ± 1.9	113.3 ± 2.1
Stage 1-2: portal fibrosis (n = 11)	165.1 ± 5.7 (1.8)	162.2 ± 6.2 (0.2)	138.9 ± 3.1 (2.1)	139.5 ± 3.3 (0.7)	111.8 ± 3.4 (1.7)	112.3 ± 3.5 (0.9)
Stage 3-4: bridging fibrosis (n = 11)	150.1 ± 3.0 (10.8)*	152.3 ± 2.8 (8.6)*	127.2 ± 1.8 (10.4)†	128.2 ± 1.7 (8.8)*	102.5 ± 2.4 (9.9)*	102.1 ± 2.4 (9.9)*
Stage 5-6: cirrhosis (n = 11)	139.8 ± 4.4 (16.9)†	140.6 ± 4.8 (15.6)†	120.9 ± 3.6 (14.8)†	122.2 ± 3.5 (13.0)†	97.6 ± 4.2 (14.2)†	95.5 ± 4.4 (15.4)†
	$P < .001$	$P < .001$	$P < .001$	$P < .001$	$P = .002$	$P = .001$
Grade categories						
Control (n = 11)	168.2 ± 3.3	166.6 ± 3.5	141.9 ± 1.6	140.5 ± 1.8	113.7 ± 1.9	113.3 ± 2.1
Grade 1-6 (n = 15)	158.6 ± 5.0 (5.7)	160.9 ± 5.1 (3.4)	134.6 ± 2.8 (5.1)	134.7 ± 3.0 (4.1)	106.5 ± 2.7 (6.3)	107.0 ± 2.9 (5.6)
Grade 7-12 (n = 12)	150.4 ± 3.6 (10.6)*	151.1 ± 3.8 (9.3)*	128.0 ± 2.4 (9.8)†	129.6 ± 2.3 (7.8)*	104.5 ± 3.5 (8.0)	103.7 ± 3.4 (8.5)
Grade 13-18 (n = 6)	136.9 ± 6.5 (18.6)†	137.0 ± 6.5 (17.8)†	117.3 ± 5.5 (17.4)†	118.7 ± 5.4 (15.5)†	96.4 ± 6.9 (15.2)*	94.0 ± 7.4 (17.1)*
	$P = .002$	$P = .003$	$P = .001$	$P = .001$	$P = .031$	$P = .018$

* $P < .05$.
† $P < .01$, when compared with the control group.
[a] Small (100 mm^2) or large (200 mm^2) regions of interest.
[b] Percentage of deviation from the control group.
[c] P values are derived from analysis of variances for comparison of the average ADC among the stage or grade categories in each column.

MR elastography is highly sensitive and specific in discriminating different stages of hepatic fibrosis in chronic viral hepatitis. The areas under the ROC curve for elasticity and viscosity were 0.997 and 0.962, respectively, at METAVIR fibrosis scores greater than or equal to F3 [27].

DW-MRI takes into account the microcirculation of blood (perfusion) and molecular Brownian motion of water (diffusion) in liver parenchyma [28]. Muller et al [29] measured a mean (± SEM) ADC value of 0.9-1.2 $\times$ 10^{-3} mm^2/s in patients with cirrhosis vs 1.39 ± 0.16 $\times$ 10^{-3} mm^2/s in healthy controls by using a maximal b value of 454 mm^2/s. Girometti et al [11] reported the mean (± SEM) ADC of 1.11 ± 0.16 $\times 10^{-3}$ mm^2/s in patients with cirrhotic livers compared with a mean ADC of 1.54 ± 0.12 $\times$ 10^{-3} mm^2/s in controls by using a maximal b value of 800 mm^2/s [11]. The discrepancies in results arise from several factors, including patient populations and imaging settings such as echo time values, but the most influencing factor is indeed the adopted b values. Previous studies have used a wide range of maximum b values, from 55-1200 s/mm^2 [30,31]. In fact, the b value reflects the effectiveness of the diffusion-probing gradients, which are applied in a diffusion-weighted sequence. As a rule, higher b values correlate with lower ADCs, which are underestimated due to the gradient-enhanced signal degradation that eliminates fast-diffusion contributions. In contrast, lower b values result in higher ADCs, which are overestimated as a consequence of signal contribution from other intravoxel incoherent motions [10]. Some researchers recommend using higher b values to approach the ADC to the true diffusion coefficient, based upon the assumption that, at lower b values, the effect of perfusion contributes to the ADCs of abdominal organs, including liver parenchyma [32]. However, the other researchers argue that lower maximum b values would improve the signal-to-noise ratio in the liver [33]. Girometti et al [16] conducted a study to evaluate liver fibrosis by using 2 consecutive diffusion-weighted experiments with 2 different maximal b values of 400 and 800 s/mm^2. They found a lower mean (± SEM) ADC in cirrhotic livers vs noncirrhotic ones, expected by using either the first (b = 400 s/mm^2; 1.14 ± 0.20 $\times 10^{-3}$ mm^2 /s vs 1.54 ± 0.12 $\times 10^{-3}$ mm^2/s) or second sequence (b = 800 s/mm^2; 0.91 ± 0.18 $\times 10^{-3}$ mm^2/s vs 1.04 ± 0.18 $\times 10^{-3}$ mm^2/s). However, ROC analysis showed that the second sequence had significantly lower accuracy, sensitivity, specificity, and positive and negative predictive values compared with the first sequence in terms of quantifying liver fibrosis. Finally, they suggested that high b values would be less reliable in discrimination between normal and fibrotic livers [16]. In another study, the AUCs of 0.913, 0.825, and 0.794 was obtained for determining HAI of 3 or higher by using maximal b values of 500, 1000, and 200 s/mm^2, respectively. These results show a better performance for b = 500 [34]. However, in a different study, which compared 5 different b values (100, 300, 500, 800, and 1000 s/mm^2), the best negative correlation between ADC value and stage of fibrosis was obtained at the b value of 800 mm^2/s [35]. In the present study, in line with

Table 2
The association between apparent diffusion coefficients ($\times 10^{-5}$ mm^2/s) values and stages of fibrosis and grade of inflammation in different b values and small or large regions of interest

	b Value (s/mm^2)[a]					
	500		700		1000	
	Small	Large	Small	Large	Small	Large
Stage	−0.618‡	−0.599‡	−0.588‡	−0.566†	−0.492†	−0.510†
Grade	−0.521†	−0.486†	−0.443†	−0.471†	−0.273*	−0.340*

* $P < .05$.
† $P < .01$.
‡ $P < .001$.
[a] Small (100 mm^2) or large (200 mm^2) regions of interest.

Girometti et al [16], we found that increasing the b value would lead to a worse performance in determining liver fibrosis. Also, the association between the ADC values and the stage of fibrosis was stronger in the b value of 500 than of 1000 s/mm^2.

Several researchers have described a decreased level of perfusion in fibrotic livers [36,37]. Annet et al [38], in a rat study, compared the ADC of liver parenchyma in rats that had liver fibrosis with normal rats. As expected, they found that ADC was lower in fibrotic livers compared with normal livers. But, interestingly, they could not observe this phenomenon when comparing the ADC on dead animals, which do not have the effect of perfusion in their liver [38]. Taken together, it is suggested that ADC is probably, to a greater extent, a function of decreased perfusion rather than restricted Brownian motion of water molecules due to collagen deposition in extracellular environment.

It is notable that most of previous studies compared DW-MRI with a simple 4-stage and 4-grade scoring system, Batts-Ludwig classification. Although this classification is simple and easily reproducible, it lacks the clarity of verbal description, which can lead to confusion for less-experienced clinicians. In this study, we used HAI as our classification, which is a more elaborative system for clinical and pathologic evaluations due to the abundance of descriptive details [23]. In a study that used HAI, the optimal ADC cut point of 1.31×10^{-3} mm^2/s, at maximal b = 400 s/mm^2, showed sensitivity and specificity of 92.9% and 100%, respectively, in discrimination of liver cirrhosis [11]. In the present study, the optimal cut point of 153.4 for ADC ($\times 10^{-5}$ mm^2/s) at a b value of 500 s/mm^2 could determine cirrhosis or bridging fibrosis with a sensitivity of 96% and specificity of 82%.

Accurate quantification of liver fibrosis in patients with chronic hepatitis is mandatory to avoid adverse effects of unnecessary antiviral treatment or a lack of necessary treatment [23]. Therefore, researchers have mainly focused their studies on finding a correlation between the results of their noninvasive methods and the stages of liver fibrosis. In this study, we observed a significant and independent correlation between the mean ADC and the stage of liver fibrosis. The association between the grade of necroinflammatory activity and ADC was not, however, independent, and totally disappeared after adjustment for stage of fibrosis. Koinuma et al [10], by using a maximum b value of 128 s/mm^2, in line with our findings, showed a significant negative correlation between ADC and stage of fibrosis but could not show any correlation between ADC and the grade of necroinflammatory changes. In another study, Taouli et al [13] also found a negative correlation between ADC and the stage of fibrosis, but a weaker negative correlation also was found between ADC and grade of necroinflammation.

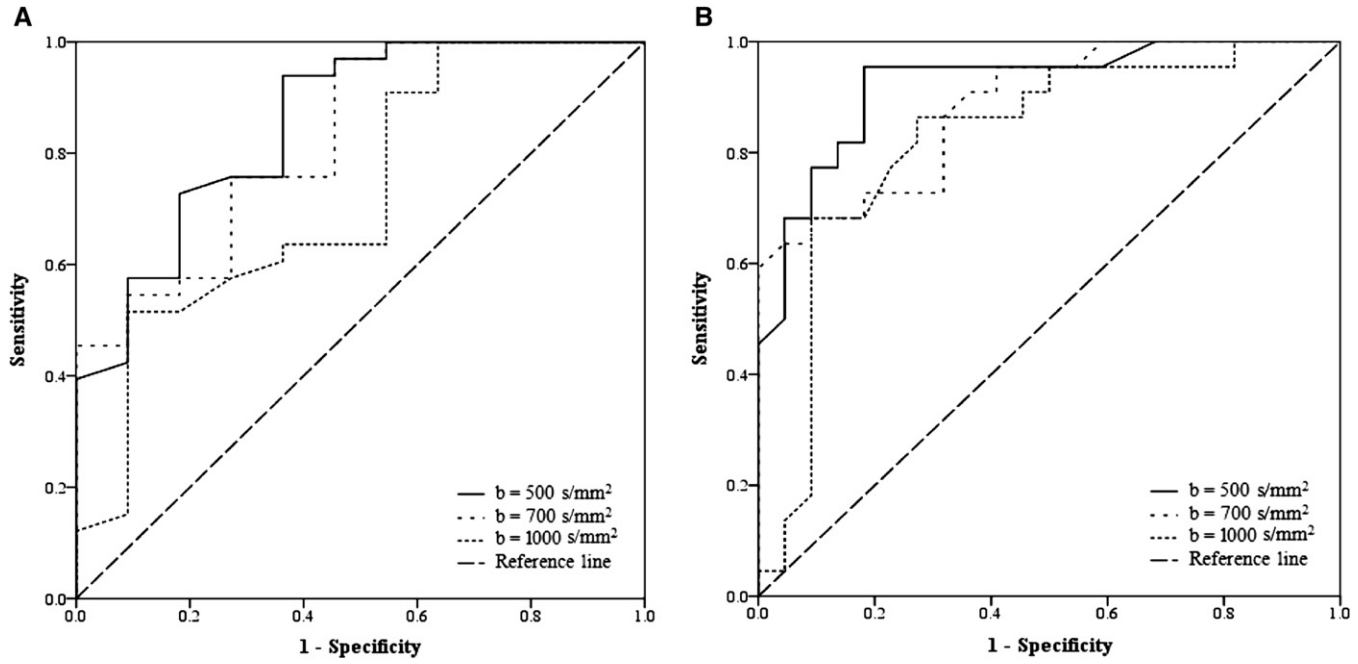

Figure 2. (A) Receiver-operating characteristic curves for performance of apparent diffusion coefficients values ($\times 10^{-5}$ mm^2/s) in determining stage ≥ 5 (cirrhosis). (B) Stage ≥ 3 (cirrhosis or bridging fibrosis) in different b values (s/mm^2) by using small regions of interest.

Table 3
The performance of ADC ($\times 10^{-5}$ mm^2/s) for determining cirrhosis and bridging fibrosis in different b values (s/mm^2), when using small ROIs

b Values	AUC ± SEM	ADC cut point	% Sensitivity	% Specificity	PLR	NLR
Cirrhosis (stage ≥ 5)						
500	0.86 ± 0.06‡	147.5	74	82	4.1	0.3
700	0.81 ± 0.07†	129.5	72	73	2.7	0.4
1000	0.72 ± 0.09*	102.2	63	62	1.6	0.6
Cirrhosis or bridging fibrosis (stage ≥ 3)						
500	0.92 ± 0.04‡	153.4	96	82	5.3	0.05
700	0.88 ± 0.05‡	134.2	89	72	3.2	0.2
1000	0.79 ± 0.07‡	107.8		72	3.0	0.2

ADC = apparent diffusion coefficient; AUC = area under the curve; NLR = negative likelihood ratio; PLR = positive likelihood ratio; ROI = region of interest; SEM = standard error of the mean.
* $P < .05$.
† $P < .01$.
‡ $P < .001$.

Previous studies have used different ROIs, which ranged from 0.5-1.73 cm^2 for calculating the ADC [11,16–18]. However, no evidence is available to identify what extent of ROI is sufficient to discriminate liver fibrosis. In this study, we did not find any significant difference in performance of a large or small ROI in terms of identifying liver fibrosis. In fact, our study showed that an ROI of 1 cm^2 would be sufficient for determining liver fibrosis.

This study has some limitations. We should note that we could perform a more in-depth analysis in each of the 6 stages of liver fibrosis if we had a larger sample size. Because of the limited numbers of available patients, we assigned each 2 neighbouring stages into one category. Nonetheless, this classification is clinically relevant; for example, the presence of bridging fibrosis (stage 3 or higher of HAI) is significant for starting the antiviral treatment, and stage 5 and 6 shows almost untreatable cirrhosis [23]. Besides, in this study, we used 3 maximal b values, and we showed a decreasing trend for performance of determining liver fibrosis when using higher vs lower b values. To determine the most appropriate b value in discriminating stages of liver fibrosis, we encourage future studies to also compare the performance of b = 500, with lower maximum b values. A major limitation of the study is the use of single b values in calculating the ADC values. Modern MR scanners can simultaneously obtain multiple b values during a single DWI acquisition, and, because ADC is calculated from the slope of a diffusion signal plotted against b value, the ADC becomes much more accurate when using multiple b values. Therefore, we encourage future studies to use ADC values obtained from multiple b values. We should mention that our results are valid with our protocol. In fact, there are many variables in the type of DW-MRI sequences that would likely alter the results, and larger trials that involve different MR and different sequences would be necessary to validate these results. In this study, we only enrolled patients with chronic viral hepatitis only. Although, as an advantage, this can lead to a more homogeneous sample of patients for this study, it could be interesting to have these data in patients with other causes of liver fibrosis. In addition, as we know, patients with chronic viral hepatitis may need several liver biopsies through their follow-up and treatment, so follow-up DW-MRI in an individual patient and evaluating the correlation of ADC values with the changes in stage of liver fibrosis may show promising results. The time frame for this study prevented us from including the follow-up data of patients; we will go through this assessment later, if possible. As an advantage, in our sample, there was no difference in the age of healthy controls and patients in different stages of liver fibrosis. Because some age-related changes may be observed in liver parenchyma of older subjects, this point has been regarded as a drawback of some studies, which could not adjust for this potential confounder [11,16].

In summary, this study showed that using either a small ROI of 100 mm^2 or a large ROI of 200 mm^2 would not result in a significant difference in performance of DW-MRI in diagnosing liver fibrosis. Also, our results showed that a b = 500 s/mm^2 is better in performance than b = 1000 s/mm^2 for determining cirrhosis or bridging fibrosis. This study provided beneficial data for choosing the more appropriate b values and the sufficient ROIs for clinical utilisation of DW-MRI in diagnosis of liver fibrosis.

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